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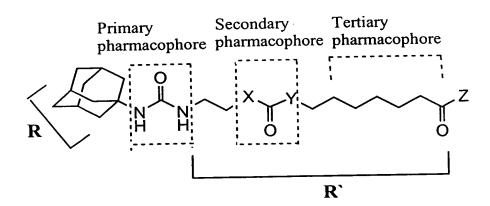
Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE HYDROLASE

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Figure 1

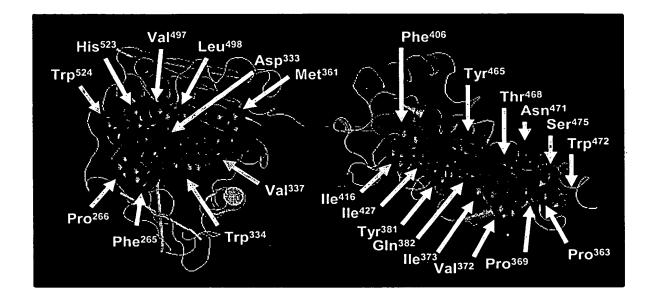
X: NH, O, or CH₂

R and R': alkyl or aryl groups



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Figure 4

Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	MTLRGAVFDLDGVLALPAVFGVLGRTEEALAL RGLLNDA MALRVAAFDLDGVLALPSIAGVLRHTEEALAL RDFLLGA MALRVAAFDLDGVLALPSIAGAFRRSEEALAL RDFLLGA M	40 40 40 22	
Himman sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	FQKGGPEGATTRLMKGEITLSQWIPLMEENCRKCSETAKV FQMKFPEGPTEQLMKGKITFSQWVPLMDESCRKSSKACGA YQTEFPEGPTEQLMKGKITFSQWVPLMDESYRKSSKACGA NIWCVGQEGPSQEDTDTIHTSEWVPLMDESYRKSSKACGA	80 80 80 62	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	CLPKNFSIKEIFDKAISARKINRPMLQAALMLRKKGFTTA SLPENFSISEIFSQAMAARSINRPMLQAAAALKKKGFTTC NLPENFSISQIFSQAMAARSINRPMLQAAIALKKKGFTTC NLPENFSISQIFSQAMAARSINRPMLQAAIALKKKGFTTC	120 120 120 102	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	ILTNTWLDDRAERDGLAQLMCELKMHFDFLIESCQVGMVKIVTNNWLDDSDKRDILAQMMCELSQHFDFLIESCQVGMIKIVTNNWLDDGDKRDSLAQMMCELSQHFDFLIESCQVGMIKIVTNNWLDDGDKRDSLAQMMCELSQHFDFLIESCQVGMIK	160 160 160 142	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	PEPQIYKFLLDTLKASPSEVVFLDDIGANLKPARDLGMVTPEPQIYKFVLDTLKAKPNEVVFLDDFGSNLKPARDMGMVTPEPQIYNFLLDTLKAKPNEVVFLDDFGSNLKPARDMGMVTPEPQIYNFLLDTLKAKPNEVVFLDDFGSNLKPARDMGMVT	200 200 200 182	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	ILVQDTDTALKELEKVTGIQLLNTPAPLPTSCNPSDMSHGILVRDTASALRELEKVTGTQFPEAPLPVPCSPNDVSHGILVHNTASALRELEKVTGTQFPEAPLPVPCNPNDVSHGILVHNTASALRELEKVTGTQFPEAPLPVPCNPNDVSHG	240 238 238 220	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	Y V T V K P R V R L H F V E L G S G P A V C L C H G F P E S W Y S W R Y Q I P A Y V T V K P G I R L H F V E M G S G P A L C L C H G F P E S W F S W R Y Q I P A Y V T V K P G I R L H F V E M G S G P A L C L C H G F P E S W F S W R Y Q I P A Y V T V K P G I R L H F V E M G S G P A L C L C H G F P E S W F S W R Y Q I P A	279 278 278 260	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238)	LAQAGFRVLAIDMKGYGESSAPPEIEEYCMEVLCKEMVTF LAQAGFRVLAIDMKGYGDSSSPPEIEEYAMELLCEEMVTF LAQAGFRVLAIDMKGYGDSSSPPEIEEYAMELLCKEMVTF LAQAGFRVLAIDMKGYGDSSSPPEIEEYAMELLCKEMVTF	319 318 318 300	
Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) Protein sequences obtained from	LDKLGLSQAVFIGHDWGGMLVWYMALFYPERVRAVASLNT LNKLGIPQAVFIGHDWAGVLVWNMALFHPERVRAVASLNT LDKLGIPQAVFIGHDWAGVMVWNMALFYPERVRAVASLNT LDKLGIPQAVFIGHDWAGVMVWNMALFYPERVRAVASLNT nthe NCBI database (accession numbers) showing identical (black) and	359 358 358 340	
homologous (gray) residues in the mammalian proteins. Sites for primary (†), secondary (‡) and tertiary (°)			

pharmacophores are indicated above each sequence.

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Figure 5

	Τ.	
Human sEH (JC4711) Rat sEH (P80299)	PFIPANPNMSPLESIKANPVFDYQLYFQEPGVAEAEL EQN PLMPPNPEVSPMEVIRSIPVFNYQLYFQEPGVAEAEL EKN	399 398
Mouse liver sEH (AAA37555)	PFMPPDPDVSPMKVIRSIPVFNYQLYFQEPGVAEAEL EKN	398
Mouse ovary sEH (AAM28238)	P F M P P D P D V S P M K V I R S I P V F N Y Q L Y F Q E P G V A E A E L E K N	380
Human sEH (JC4711)	LSRTFKSLFRASDESVLSM-HKVCEAGGLFVNSPEEPSLS	438
Rat sEH (P80299)	M SRTFK SFFRTSDD MGLLTVNKATE MGGILVGTPEDP KVS	438
Mouse liver sEH (AAA37555)	M SRTFK SFFR A SDETGFIAVHKATE I GGIL VNT PEDP N L S	438
Mouse ovary sEH (AAM28238)	MSRTFKSFFRASDETGFIAVHKATE I GGILVNT PEDP N LS	420
Human sEH (JC4711)	R M V T E E E I Q F Y V Q Q F K K S G F R G P L N W Y R N M E R N W K W A C K S	478
Rat sEH (P80299)	K I T T E E E I E Y Y I Q Q F K K S G F R G P L N W Y R N T E R N W K W S C K A	478
Mouse liver sEH (AAA37555)	K IT TEEEI E FYIQQFKK T GFRGPLNWYRNTERNWKWS CKG	478
Mouse ovary sEH (AAM28238)	K <mark>IT</mark> TEEEI <mark>B</mark> FYIQQFKK <mark>T</mark> GFRGPLNWYRNTERNWKWS CKG	460
**************************************	LGRKILIPALMVTAEKDFVL <mark>VPQ</mark> MSQHMEDWIPHLKRGHI	518
Human sEH (JC4711)	LGRKILIPALMVIAEKDIVLRPEMSKNMENWIPFLKRGHI	518
Rat sEH (P80299) Mouse liver sEH (AAA37555)	LGRKILVPALMVTAEKDIVLRPEMSKNMEKWIPFLKR GHI	518
Mouse ovary sEH (AAM28238)	LGRKILVPALMVTAEKDIVLRPEMSKNMEKWIPFLKR GHI	500
House Ovary SEA (AM-120236)	EGRRIE VEREN VIRERDI VEREN SKAMBRUTTE EKK GHI	300
Human sEH (JC4711)	EDCGHWTQMDKPTEVNQILIKWLDSDARNPPVVSKM	554
Rat sEH (P80299)	EDCGHWTQIEKPAEVNQILIKWLKTEIQNPSVTSKI	554
Mouse liver sEH (AAA37555)	EDCGHWTQIEKPTEVNQILIKWLQTEVQNPSVTSKI	554
Mouse ovary sEH (AAM28238)	EDCGHWTQIEKPTEVNQILIKWLQTEVQNPSVTSKI	536

Protein sequences obtained from the NCBI database (accession numbers) showing identical (black) and homologous (gray) residues in the mammalian proteins. Sites for primary (†), secondary (‡) and tertiary (°) pharmacophores are indicated above each sequence.

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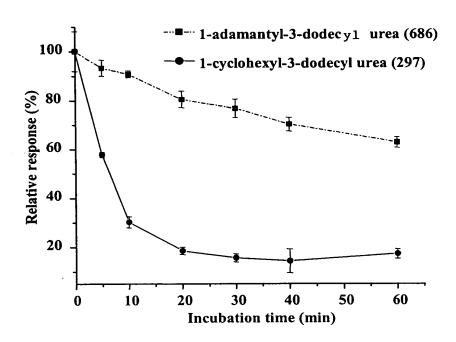
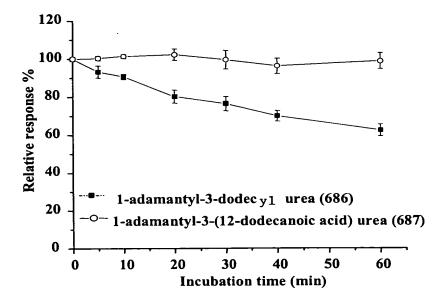
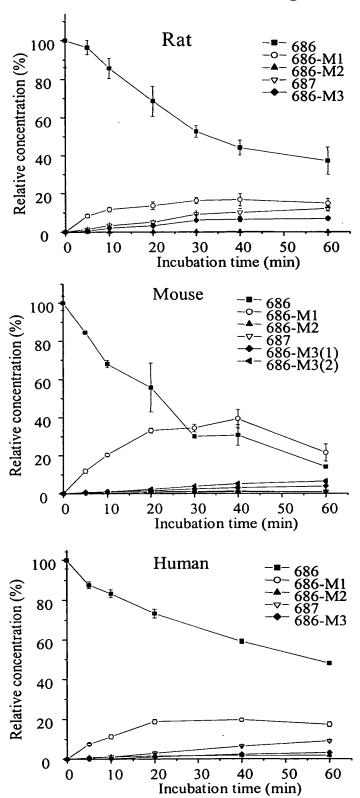


Figure 7



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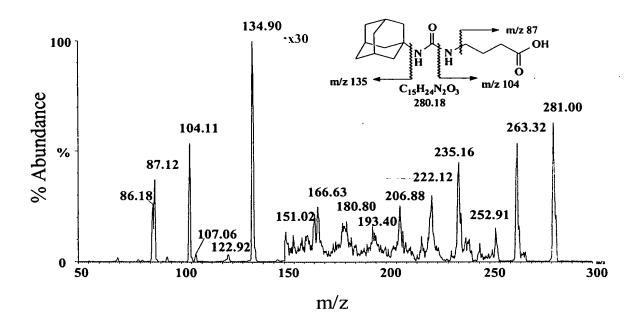
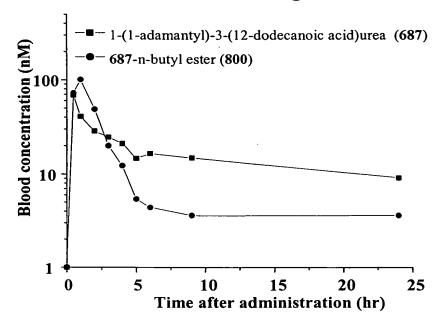
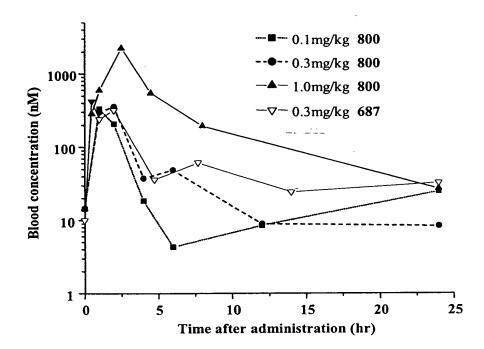


Figure 10



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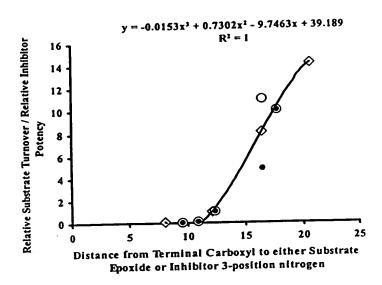
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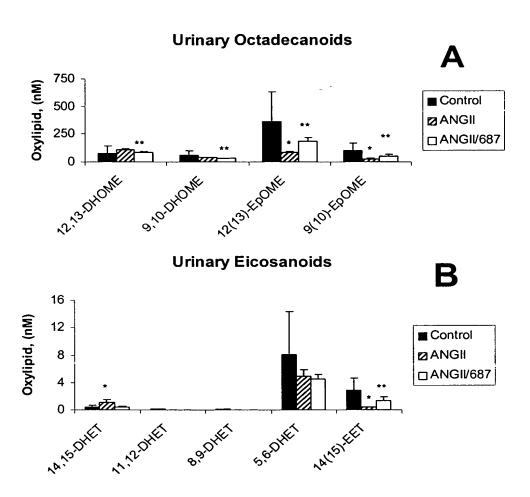


- ♦ Relative EET Turnover
- O Inhibitor Rank-order potency with Ms EH
- Inhibitor Rank-order potency with HsEH

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Figure 14



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